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~~NOTIFICATION OF TRANSMITTAL OF~~
THE INTERNATIONAL SEARCH REPORT AND
THE WRITTEN OPINION OF THE INTERNATIONAL
SEARCHING AUTHORITY, OR THE DECLARATION

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UNITED STATES OF AMERICA

(PCT Rule 44.1)

Date of mailing
(day/month/year)

23/03/2005

Applicant's or agent's file reference

297/177 PCT

FOR FURTHER ACTION

See paragraphs 1 and 4 below

International application No.

PCT/US2004/036426

International filing date
(day/month/year)

01/11/2004

Applicant

NORTH CAROLINA STATE UNIVERSITY

1. ☒ The applicant is hereby notified that the international search report and the written opinion of the International Searching Authority have been established and are transmitted herewith.

Filing of amendments and statement under Article 19:

The applicant is entitled, if he so wishes, to amend the claims of the international Application (see Rule 46):

When? The time limit for filing such amendments is normally 2 months from the date of transmittal of the International Search Report; however, for more details, see the notes on the accompanying sheet.

Where? Directly to the International Bureau of WIPO, 34 chemin des Colombettes
1211 Geneva 20, Switzerland, Facsimile No.: (41-22) 740.14.35

For more detailed instructions, see the notes on the accompanying sheet.

2. ☐ The applicant is hereby notified that no International search report will be established and that the declaration under Article 17(2)(a) to that effect and the written opinion of the International Searching Authority are transmitted herewith.

3. ☐ With regard to the protest against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that:

- ☐ the protest together with the decision thereon has been transmitted to the International Bureau together with the applicant's request to forward the texts of both the protest and the decision thereon to the designated Offices.
- ☐ no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.

4. Reminders

Shortly after the expiration of 18 months from the priority date, the international application will be published by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the international application, or of the priority claim, must reach the International Bureau as provided in Rules 90bis.1 and 90bis.3, respectively, before the completion of the technical preparations for international publication.


The applicant may submit comments on an informal basis on the written opinion of the International Searching Authority to the International Bureau. The International Bureau will send a copy of such comments to all designated Offices unless an international preliminary examination report has been or is to be established. These comments would also be made available to the public but not before the expiration of 30 months from the priority date.

Within **19 months** from the priority date, but only in respect of some designated Offices, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase until **30 months** from the priority date (in some Offices even later); otherwise, the applicant must, **within 20 months** from the priority date, perform the prescribed acts for entry into the national phase before those designated Offices.

In respect of other designated Offices, the time limit of **30 months** (or later) will apply even if no demand is filed within 19 months.

See the Annex to Form PCT/IB/301 and, for details about the applicable time limits, Office by Office, see the *PCT Applicant's Guide*, Volume II, National Chapters and the WIPO Internet site.

Name and mailing address of the International Searching Authority



European Patent Office, P.B. 5818 Patentlaan 2
NL-2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer _____

DOCKET DATES: _____
 Anna Guerin ASSIGNED ATTY: ATTJNC
 FILE NO. 297/177 PCT
 DOCKETED BY: HMD
 DATE: 4/10 (See notes on accompanying sheet)

Form PCT/ISA/220 (January 2004)

NOTES TO FORM PCT/ISA/220

These Notes are intended to give the basic instructions concerning the filing of amendments under article 19. The Notes are based on the requirements of the Patent Cooperation Treaty, the Regulations and the Administrative Instructions under that Treaty. In case of discrepancy between these Notes and those requirements, the latter are applicable. For more detailed information, see also the PCT Applicant's Guide, a publication of WIPO.

In these Notes, "Article", "Rule", and "Section" refer to the provisions of the PCT, the PCT Regulations and the PCT Administrative Instructions respectively.

INSTRUCTIONS CONCERNING AMENDMENTS UNDER ARTICLE 19

The applicant has, after having received the international search report, one opportunity to amend the claims of the international application. It should however be emphasized that, since all parts of the international application (claims, description and drawings) may be amended during the international preliminary examination procedure, there is usually no need to file amendments of the claims under Article 19 except where, e.g. the applicant wants the latter to be published for the purposes of provisional protection or has another reason for amending the claims before international publication. Furthermore, it should be emphasized that provisional protection is available in some States only.

What parts of the international application may be amended?

Under Article 19, only the claims may be amended.

During the international phase, the claims may also be amended (or further amended) under Article 34 before the International Preliminary Examining Authority. The description and drawings may only be amended under Article 34 before the International Examining Authority.

Upon entry into the national phase, all parts of the international application may be amended under Article 28 or, where applicable, Article 41.

When?

Within 2 months from the date of transmittal of the international search report or 16 months from the priority date, whichever time limit expires later. It should be noted, however, that the amendments will be considered as having been received on time if they are received by the International Bureau after the expiration of the applicable time limit but before the completion of the technical preparations for international publication (Rule 46.1).

Where not to file the amendments?

The amendments may only be filed with the International Bureau and not with the receiving Office or the International Searching Authority (Rule 46.2).

Where a demand for international preliminary examination has been filed, see below.

How?

Either by cancelling one or more entire claims, by adding one or more new claims or by amending the text of one or more of the claims as filed.

A replacement sheet must be submitted for each sheet of the claims which, on account of an amendment or amendments, differs from the sheet originally filed.

All the claims appearing on a replacement sheet must be numbered in Arabic numerals. Where a claim is cancelled, no renumbering of the other claims is required. In all cases where claims are renumbered, they must be renumbered consecutively (Administrative Instructions, Section 205(b)).

The amendments must be made in the language in which the international application is to be published.

What documents must/may accompany the amendments?

Letter (Section 205(b)):

The amendments must be submitted with a letter.

The latter will not be published with the international application and the amended claims. It should not be confused with the "Statement under Article 19(1)" (see below, under "Statement under Article 19(1)").

The letter must be in English or French, at the choice of the applicant. However, if the language of the international application is English, the letter must be in English; if the language of the international application is French, the letter must be in French.

NOTES TO FORM PCT/ISA/220 (continued)

The letter must indicate the differences between the claims as filed and the claims as amended. It must, in particular, indicate, in connection with each claim appearing in the international application (it being understood that identical indications concerning several claims may be grouped), whether

- (i) the claim is unchanged;
- (ii) the claim is cancelled;
- (iii) the claim is new;
- (iv) the claim replaces one or more claims as filed;
- (v) the claim is the result of the division of a claim as filed.

The following examples illustrate the manner in which amendments must be explained in the accompanying letter:

1. [Where originally there were 48 claims and after amendment of some claims there are 51]:
"Claims 1 to 29, 31, 32, 34, 35, 37 to 48 replaced by amended claims bearing the same numbers; claims 30, 33 and 36 unchanged; new claims 49 to 51 added."
2. [Where originally there were 15 claims and after amendment of all claims there are 11]:
"Claims 1 to 15 replaced by amended claims 1 to 11."
3. [Where originally there were 14 claims and the amendments consist in cancelling some claims and in adding new claims]:
"Claims 1 to 6 and 14 unchanged; claims 7 to 13 cancelled; new claims 15, 16 and 17 added." or
"Claims 7 to 13 cancelled; new claims 15, 16 and 17 added; all other claims unchanged."
4. [Where various kinds of amendments are made]:
"Claims 1-10 unchanged; claims 11 to 13, 18 and 19 cancelled; claims 14, 15 and 16 replaced by amended claim 14; claim 17 subdivided into amended claims 15, 16 and 17; new claims 20 and 21 added."

"Statement under Article 19(1)" (Rule 46.4)

The amendments may be accompanied by a statement explaining the amendments and indicating any impact that such amendments might have on the description and the drawings (which cannot be amended under Article 19(1)).

The statement will be published with the international application and the amended claims.

It must be in the language in which the international application is to be published.

It must be brief, not exceeding 500 words if in English or if translated into English.

It should not be confused with and does not replace the letter indicating the differences between the claims as filed and as amended. It must be filed on a separate sheet and must be identified as such by a heading, preferably by using the words "Statement under Article 19(1)".

It may not contain any disparaging comments on the international search report or the relevance of citations contained in that report. Reference to citations, relevant to a given claim, contained in the international search report may be made only in connection with an amendment of that claim.

Consequence if a demand for international preliminary examination has already been filed

If, at the time of filing any amendments under Article 19, a demand for international preliminary examination has already been submitted, the applicant must preferably, at the same time of filing the amendments with the International Bureau, also file a copy of such amendments with the International Preliminary Examining Authority (see Rule 62.2(e), first sentence).

Consequence with regard to translation of the international application for entry into the national phase

The applicant's attention is drawn to the fact that, where upon entry into the national phase, a translation of the claims as amended under Article 19 may have to be furnished to the designated/elected Offices, instead of, or in addition to, the translation of the claims as filed.

For further details on the requirements of each designated/elected Office, see Volume II of the PCT Applicant's Guide.

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference 297/177 PCT	FOR FURTHER ACTION		see Form PCT/ISA/220 as well as, where applicable, item 5 below.
International application No. PCT/US2004/036426	International filing date (day/month/year) 01/11/2004	(Earliest) Priority Date (day/month/year) 30/10/2003	
Applicant NORTH CAROLINA STATE UNIVERSITY			

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 4 sheets.

☒ It is also accompanied by a copy of each prior art document cited in this report.

1. Basis of the report

- a. With regard to the language, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

☐ The international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

- b. ☐ With regard to any nucleotide and/or amino acid sequence disclosed in the international application, see Box No. I.

2. ☐ Certain claims were found unsearchable (See Box II).3. ☐ Unity of invention is lacking (see Box III).

4. With regard to the title,

☒ the text is approved as submitted by the applicant.

☐ the text has been established by this Authority to read as follows:

5. With regard to the abstract,

☒ the text is approved as submitted by the applicant.

☐ the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box No. IV. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. With regard to the drawings,

- a. the figure of the drawings to be published with the abstract is Figure No. 1b

☐ as suggested by the applicant.

☐ as selected by this Authority, because the applicant failed to suggest a figure.

☒ as selected by this Authority, because this figure better characterizes the invention.

- b. ☐ none of the figures is to be published with the abstract.

INTERNATIONAL SEARCH REPORT

International Application No.
PCT/US2004/036426

A. CLASSIFICATION OF SUBJECT MATTER IPC 7 C12Q1/68		
According to International Patent Classification (IPC) or to both national classification and IPC		
B. FIELDS SEARCHED		
Minimum documentation searched (classification system followed by classification symbols) IPC 7 C12Q		
Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched		
Electronic data base consulted during the international search (name of data base and, where practical, search terms used) EP0-Internal, WPI Data, PAJ, BIOSIS, EMBASE, CHEM ABS Data		
C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P, X	LOWE L B ET AL: "Laser-induced temperature jump electrochemistry on gold nanoparticle-coated electrodes" JOURNAL OF THE AMERICAN CHEMICAL SOCIETY, AMERICAN CHEMICAL SOCIETY, WASHINGTON, DC, US, vol. 125, no. 47, 26 November 2003 (2003-11-26), pages 14258-14259, XP002316112 ISSN: 0002-7863 the whole document ----- -/--	1-38
<input checked="" type="checkbox"/> Further documents are listed in the continuation of box C. <input checked="" type="checkbox"/> Patent family members are listed in annex.		
* Special categories of cited documents: *A* document defining the general state of the art which is not considered to be of particular relevance *E* earlier document but published on or after the international filing date *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) *O* document referring to an oral disclosure, use, exhibition or other means *P* document published prior to the international filing date but later than the priority date claimed *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone ** document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art *S* document member of the same patent family		
Date of the actual completion of the international search 16 March 2005		Date of mailing of the international search report 23/03/2005
Name and mailing address of the ISA European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel (+31-70) 340-2040, Tx. 31 651 epo nl, Fax (+31-70) 340-3016		Authorized officer Mueller, F

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US2004/036426

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	PARK S-J ET AL: "ARRAY-BASED ELECTRICAL DETECTION OF DNA WITH NANOPARTICLE PROBES" SCIENCE, AMERICAN ASSOCIATION FOR THE ADVANCEMENT OF SCIENCE,, US, vol. 295, 22 February 2002 (2002-02-22), pages 1503-1506, XP001160895 ISSN: 0036-8075 the whole document -----	1-38
X	WO 99/51778 A (CALIFORNIA INSTITUTE OF TECHNOLOGY; BARTON, JACQUELINE; HILL, MICHAEL;) 14 October 1999 (1999-10-14) the whole document -----	1-38
X	WO 98/04740 A (NORTHWESTERN UNIVERSITY; MIRKIN, CHAD, A; LETSINGER, ROBERT, L; MUCIC,) 5 February 1998 (1998-02-05) see whole doc. esp. claims and figures -----	1-38

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US2004/036426

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9951778 A	14-10-1999	US 6221586 B1	24-04-2001
		AU 3550699 A	25-10-1999
		EP 1068359 A1	17-01-2001
		JP 2002510791 T	09-04-2002
		WO 9951778 A1	14-10-1999
		US 2004063126 A1	01-04-2004
		US 2002055103 A1	09-05-2002
		US 2002146716 A1	10-10-2002
WO 9804740 A	05-02-1998	AU 4043497 A	20-02-1998
		CA 2262018 A1	05-02-1998
		EP 0918885 A1	02-06-1999
		JP 2000516460 T	12-12-2000
		JP 2004194669 A	15-07-2004
		US 2003087242 A1	08-05-2003
		WO 9804740 A1	05-02-1998
		US 2003207296 A1	06-11-2003
		US 6361944 B1	26-03-2002
		US 2003180783 A1	25-09-2003
		US 6506564 B1	14-01-2003
		US 6495324 B1	17-12-2002
		US 6417340 B1	09-07-2002
		US 2004110220 A1	10-06-2004
		US 2002155442 A1	24-10-2002
		US 2003022169 A1	30-01-2003
		US 2002137058 A1	26-09-2002
		US 2002172953 A1	21-11-2002
		US 2003059777 A1	27-03-2003
		US 2003049630 A1	13-03-2003
		US 2002146720 A1	10-10-2002
		US 2002164605 A1	07-11-2002
		US 2002182611 A1	05-12-2002
		US 2002155458 A1	24-10-2002
		US 2002137070 A1	26-09-2002
		US 2002127574 A1	12-09-2002
		US 2002137071 A1	26-09-2002
		US 2003049631 A1	13-03-2003
		US 2003143538 A1	31-07-2003
		US 2002155459 A1	24-10-2002
		US 2003054358 A1	20-03-2003
		US 2002160381 A1	31-10-2002
		US 2002155461 A1	24-10-2002
		US 2002155462 A1	24-10-2002
		US 2003124528 A1	03-07-2003
		US 2002137072 A1	26-09-2002
		US 6812334 B1	02-11-2004
		US 2003068622 A1	10-04-2003
		US 2004219520 A1	04-11-2004
		US 2003148282 A1	07-08-2003
		US 2002182613 A1	05-12-2002
		US 2003044805 A1	06-03-2003

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY (PCT Rule 43bis.1)

Date of mailing
(day/month/year) see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference
see form PCT/ISA/220

FOR FURTHER ACTION
See paragraph 2 below

International application No.
PCT/US2004/036426

International filing date (day/month/year)
01.11.2004

Priority date (day/month/year)
30.10.2003

International Patent Classification (IPC) or both national classification and IPC
C12Q1/68

Applicant
NORTH CAROLINA STATE UNIVERSITY

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☐ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. FURTHER ACTION

If a demand for International preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1bis(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA:



European Patent Office
D-80298 Munich
Tel. +49 89 2399 - 0 Tx: 523656 epmu d
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Authorized Officer

Mueller, F

Telephone No. +49 89 2399-7722



**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.
PCT/US2004/036426

Box No. I Basis of the opinion

1. With regard to the language, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.
 - ☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).
2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:
 - a. type of material:
 - ☐ a sequence listing
 - ☐ table(s) related to the sequence listing
 - b. format of material:
 - ☐ in written format
 - ☐ in computer readable form
 - c. time of filing/furnishing:
 - ☐ contained in the international application as filed.
 - ☐ filed together with the international application in computer readable form.
 - ☐ furnished subsequently to this Authority for the purposes of search.
3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.
4. Additional comments:

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.
PCT/US2004/036426

Box No. V Reasoned statement under Rule 43b/s.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes: Claims	1-38
	No: Claims	
Inventive step (IS)	Yes: Claims	
	No: Claims	1-38
Industrial applicability (IA)	Yes: Claims	1-38
	No: Claims	

2. Citations and explanations

see separate sheet

Re Item V.

1 Reference is made to the following documents:

D1 : PARK S-J ET AL:SCIENCE, vol. 295, 22 February 2002, pages 1503-1506

D2 : WO 99/51778 A

D3 : WO 98/04740 A

The subject-matter of claim 1 is not inventive (Article 33(3) PCT).

Present claim 1 describes a method for detecting target sequences by the use of a capture probe immobilized onto an electrode, nanoparticle-labelled target molecules and the use of an redox solution which induces an electrical signal in the electrode.

D1, a document in the field of detecting nucleic acid hybridization, describes the use of capture probes which are immobilized onto an electrode and hybridized to complementary target sequences which comprise an attached nanoparticle. The hybridization of the two nucleic acid strands are measured by the use of an AgNO₃/hydroquinone solution, see p.1504, 1. col., 2. par.. The method of D1 therefore is considered to provide already a method which enables the detection of target/probe hybridization by the use of an electrode.

D2, a document in the field of electrochemical sensors, describes a method for detecting target sequences by forming nucleic acid duplexes onto an electrode surface and by adding an intercalative redox-active compound which enables the measurement of an electron transfer, see e.g. claims and examples. The disclosure of D2 is considered to already provide a method for the detection of target sequences with the use of an electrode.

D3, a document in the field nanoparticles and nucleic acid detection, already provides a method for the detection of target/probe hybridization by using nanoparticles, see e.g. figures and claims.

All the essential technical features of present claim 1 are already provided in the prior art (D1-D3), furthermore no special technical effect of the present claimed method could be

identified in comparison with the prior art (D1-D3) which would allow the acknowledgement of an inventive step. Article 33(3) PCT is thus not fulfilled.
The same holds true for thereon dependent claims 2-38.

The following has also to be considered:

- The wording "sacrificial" in claim 32 is considered not to be a technical expression and therefore renders the scope of the claim unclear (Article 6 PCT).
- The vague and imprecise statement "It will be understood..." in the description on page 58, lines 12-15, implies that the subject-matter for which protection is sought may be different to that defined by the claims, thereby resulting in a lack of clarity (Article 6 PCT) when used to interpret them (see also PCT Guidelines, C-III, 4.3).
- Contrary to the requirements of Rule 5.1(a)(ii) PCT, the relevant background art disclosed in the documents D1-D3 is not mentioned in the description, nor is/are this/these documents identified therein.